ABSTRACT

The present invention relates to the discovery that non-traditional export of certain pro-inflammatory cytokines lacking a signal sequence from a cell can be inhibited by copper chelation and/or administration to the cell of a truncated form of S100A13 lacking the basic residue portion. Further, copper chelation inhibits, inter alia, neointima formation, macrophage infiltration and associated inflammation, cell proliferation, secretion of extracellular matrix, intimal thickening, adventitial angiogenesis, restenosis, and the like, associated with vascular vessel injury. Thus, the present invention provides novel methods of preventing and treating, and for identifying novel compounds also useful as therapeutics for, such conditions.

COPPER-DEPENDENT NON-TRADITIONAL PRO-INFLAMMATORY CYTOKINE EXPORT AND METHODS, COMPOSITIONS AND KITS RELATING THERETO

BACKGROUND OF THE INVENTION

[0001] The prototype members of the interleukin 1 (IL1) and fibroblast growth factor (FGF) gene families are well recognized for their receptor-dependent inflammatory and angiogenic activities in vitro and in vivo (Dinarello, 1994, FASEB J. 8:1314-1325; Krakauer, 1986, Crit. Rev. Immunol. 6:213-244; Dinarello, 1998, Int. Rev. Immunol. 16:457-499; Maini and Taylor, 2000, Annu. Rev. Med. 51:207-229; Blum and Miller, 2001, Annu. Rev. Med. 52:15-27; Burgess and Maciag, 1989, Annu. Rev. Med. 58:575-606; Friesel and Maciag, 1999, Thromb. Haemost. 82:748-754; McKeehan et al., 1998, Prog. Nucleic Acid Res. Mol. Biol. 59:135-176; Vlodavsky et al. 1996, Cancer Metastasis Rev. 15:177-186), yet the prototypes lack a signal peptide sequence to direct their export through the classical secretion pathway mediated by the endoplasmic reticulum-Golgi apparatus (Jaye et al., 1986, Science 233:541-545; Abraham et al., 1986, Science 233:545-548; Lomedico et al., 1984, Nature 312:458-462). Interestingly, crystallographic studies have demonstrated that the prototype members of the IL1 and FGF gene families exhibit a high level of structural homology (Carter et al., 1988, Proteins 3:121-129; Zhang et al., 1991, Proc. Natl. Acad. Sci. USA 88:3446-3450, Zhu et al., 1991, Science 251:90-93; Erikson et al., 1991, Proc. Natl. Acad. Sci. USA 88:3441-3445) despite their unremarkable sequence similarities (Thomas et al., 1985, Proc. Natl. Acad. Sci. USA 82:6409-6413). While the FGF gene family evolved only three genes lacking a signal peptide sequence (Burgess and Maciag, 1989, Annu. Rev. Med. 58:575-606; Friesel and Maciag, 1999, Thromb. Haemost. 82:748-754; McKeehan et al., 1998, Prog. Nucleic Acid Res. Mol. Biol. 59:135-176), eight of the ten members of the IL1 gene family lack this structural feature (Smith, et al. 2000; Kumar, et al. 2000). Thus, it is important to understand and define the non-classical pathways utilized by these signal peptide-less cytokines for export since this information may ultimately prove to be valuable for the clinical management of inflammatory and angiogenic-dependent events.

[0002] The release of the FGF1 and IL1α prototypes is regulated by convergent yet distinct pathways which utilize cellular stress to mediate export of these polypeptides into the extracellular compartment (Tarantini et al., 2001, J. Biol. Chem. 276:5147-5151; Tarantini et al., 1995, J. Biol. Chem. 270:29039-29042). It is known that FGF1 is released in response to stress as a latent homodimer which requires intracellular oxidation of a conserved cysteine residue at position 30 (Tarantini et al., 1995). This event enables FGF1 to interact with the extravesicular